Epidemiology and Infection:

Predicting treatment failure, death and drug resistance using a computed risk score among newly-diagnosed TB patients in Tamaulipas, Mexico

B. E. Abdelbary, M. Garcia-Viveros, H. Ramirez-Oropesa, M.H. Rahbar, B.I. Restrepo

**Characteristics of TB patients with adverse outcomes and drug resistance in the derivation data set**

TB patients who failed their initial treatment regimen with first line antibiotics (versus no treatment failure) were males (71%) with no or primary school education (70%), more likely to present with an initial positive AFB smear (92.2%) and 31% had MDR TB. On the other hand, TB patients who died during treatment (versus no death) were significantly older, more likely to be males (79.3%), with education at or below primary school level (66%), reporting excess alcohol use (11.1%), less likely to be BCG vaccinated, and more than 50% were either not employed or unemployed (34.8% and 20.6% respectively). On evaluating their clinical profile, TB patients who died more likely to present with extra-pulmonary TB (14.6%), had HIV (19.2%) or malnutrition (20.3%) and were less likely to have initial positive AFB smear (78.2%) or present with diabetes as a co-morbidity. TB patients showing resistance to any of the five drugs tested were more likely to present with pulmonary disease (99.3%), have an initial positive AFB smear (92.7%). (Table S1)

**Characteristics of TB patients with adverse outcomes and drug resistance in the validation data set**

TB patients who failed their initial treatment regimen with first line antibiotics (versus no treatment failure) were males (76%) with no or primary school education (66%), more likely to present with an initial positive AFB smear (94.6%). On the other hand, TB patients who died during treatment (versus no death) were significantly older, more likely to be males (69.2%), with education at or below primary school level (72.8%), reporting excess alcohol use (8.9%), less likely to be BCG vaccinated, and more than 60% were either not employed or unemployed (44.7% and 25.5% respectively). On evaluating their clinical profile, TB patients who died more likely to present with extra-pulmonary TB (15%), had HIV (18.9%) or malnutrition (14.2%) and were less likely to have initial positive AFB smear (77.5%) or present with diabetes as a co-morbidity. TB patients showing resistance to any of the five drugs tested were more likely to present with pulmonary disease (99.1%), have an initial positive AFB smear (95.4%), and present with DM as comorbidity (34.2%). (Table S2)

**Summary of models and estimated proportion of TB patients that would benefit from enhanced monitoring**

After developing the cut-off, we evaluated the percent of the TB patients with scores above the cut-off points. 34.4% of all TB patients had a score equal or above 15 for treatment failure, 58.4% had a score above or equal 9 for drug resistance, and 47.6% had a score of equal or above 5 for death. (Table S3)

Table S4 delineates the percentage of TB patients with constructed risk score within each of the score categories displayed in figure 1 and the proportion of the observed adverse outcomes within each category. From table S4, we can also estimate the score and percentage of TB patients to be recommended for enhanced case management (those with high observed adverse outcomes).

**Characteristics of TB patients with adverse outcomes by score cutoff point**

We used the whole data for TB patients in Tamaulipas Mexico between 2006 and 2013 to evaluate demographic and clinical characteristics of TB patients with adverse outcomes by score cutoff point utilizing univariate regression analysis. Among the 521 patients who experienced death as their adverse outcome, those with a calculated modified risk score ≥ 5 (n=400) were more likely to be older (mean age 55, OR 1.1, 95% CI (1.0, 1.1), males (OR 4.6, 95% CI (2.9, 7.1), with no or primary school education (OR 2.2, 95% CI (1.4, 3.4), presenting with pulmonary TB (OR 1.0, 95% CI (1.1, 3.2), and malnutrition (OR 10.9, 95% CI (3.4, 35.2) and reporting excessive alcohol use (OR 17.5, 95% CI (2.4, 128.3). Among the 158 patients with documented treatment failure as their adverse outcome, those with a modified risk score ≥ 15 (n=92) were more likely to have no or primary school education (OR 2.8, 95% CI (1.3, 5.8). Among the 259 TB patients with documented drug resistance, those with a modified risk score cutoff point ≥ 9 (n=204) were more likely to be unemployed (OR 7.9, 95% CI (1.0, 61.9) and less likely to be diabetics (OR 0.3, 95% CI (0.1, 0.6) (Table S5).

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| Table S1: Demographic features and clinical presentation of 4,216 TB patients in the derivation data set by adverse outcomes and drug resistance status in Tamaulipas Mexico 2006- 2013 \* | | | | | | | | | |
|  | Death | | | Treatment failure | | | Drug Resistance | | |
| Characteristics | Yes (n=261) | No | OR (95%CI) | Yes  (n=65) | No | OR (95%CI) | Yes (n=145) | No | OR (95%CI) |
| Age (mean, ± SD) | 50.9 (18.2) | 42.7 (16.6) | **1.02 (1.02, 1.03)** | 47.9 (16) | 43.1 (16.8) | **1.0 (1.0, 1.03)** | 41.4 (15.7) | 43.2 (16.9) | 0.9 (0.9, 1.03) |
| Gender |  |  |  |  |  |  |  |  |  |
| Female | 20.7% | 34.6% | 1 | 29.2% | 33.8% | 1 | 30.3% | 33.9% | 1 |
| Male | 79.3% | 65.4% | **2.0 (1.5, 2.8)** | 70.8% | 66.2% | 1.2 (0.7, 2.1) | 69.7% | 66.1% | 1.2 (0.8, 1.7) |
| Education |  |  |  |  |  |  |  |  |  |
| Higher than primary school | 34% | 42.7% | 1 | 29.7% | 42.4% | 1 | 44.8% | 42.1% | 1 |
| No or primary school | 66% | 57.3% | **1.5 (1.1, 1.9)** | 70.3% | 57.6% | **1.7 (1.0, 2.9)** | 55.2% | 57.9% | 0.9 (0.6, 1.3) |
| Employment Status |  |  |  |  |  |  |  |  |  |
| Employed | 44.6% | 42% | 1 | 47.2% | 42% | 1 | 44% | 42.1% | 1 |
| Not employed\*\* | 34.8% | 43.2% | 0.8 (0.5, 1.1) | 43.4% | 42.7% | 0.9 (0.5, 1.6) | 36.8% | 42.9% | 0.8 (0.5, 1.2) |
| Unemployed | 20.6% | 14.8% | 1.3 (0.9, 1.9) | 9.4% | 15.3% | 0.5 (0.2, 1.4) | 19.2% | 15% | 1.2 (0.7, 1.9) |
| BCG Vaccine (yes) | 66.2% | 76.6% | **0.6 (0.5, 0.8)** | 81.7% | 75.9% | 1.4 (0.7, 2.7) | 81.3% | 75.8% | 1.3 (0.9, 2.1) |
| Location of disease |  |  |  |  |  |  |  |  |  |
| Extra-pulmonary | 14.6% | 7.3% | 1 | 0% | 7.8% | N/A | 0.7% | 8% | 1 |
| Pulmonary | 85.4% | 92.7% | **0.5 (0.3, 0.7)** | 100% | 92.2% | N/A | 99.3% | 92% | **12.5 (1.7, 89.3)** |
| MDR (yes) | 1.9% | 0.8% | 2.5 (0.9, 6.6) | 30.8% | 0.4% | **122 (58, 254)** | N/A | N/A | N/A |
| Positive initial AFB smear | 78.2% | 86.4% | **0.6 (0.4, 0.8)** | 92.2% | 85.9% | 1.9 (0.8, 4.8) | 92.7% | 85.7% | **2.2 (1.1, 4.2)** |
| Number of bacilli in initial AFB smear |  |  |  |  |  |  |  |  |  |
| Negative | 22% | 13.6% | 1 | 7.8% | 14.2% | 1 | 7.1% | 14.3% | 1 |
| Rare bacilli (+1) | 37.1% | 37% | **0.6 (0.4, 0.9)** | 26.6% | 37.2% | 1.3 (0.5, 3.5) | 29.8% | 37.3% | 1.6 (0.8, 3.2) |
| Few to moderate (> +2) | 41% | 49.4% | **0.5 (0.3, 0.7)** | 65.6% | 48.6% | 2.5 (0.9, 6.2) | 63.1% | 48.4% | **2.6 (1.3, 5.1)** |
| Comorbidities |  |  |  |  |  |  |  |  |  |
| Diabetes | 17.2% | 25.7% | **0.6 (0.4, 0.8)** | 30.8% | 25.1% | 1.3 (0.8, 2.3) | 30% | 25% | 1.2 (0.8, 1.8) |
| HIV | 19.2% | 4.4% | **5.1 (3.6, 7.2)** | 3.1 % | 5.4% | 0.6 (0.1, 2.3) | 3.5% | 5.4% | 0.6 (0.3, 1.5) |
| Malnutrition | 20.3% | 8.4% | **2.8 (2.0, 3.8)** | 12.3% | 9.1% | 1.4 (0.7, 2.9) | 8.3% | 9.2% | 0.9 (0.5, 1.6) |
| Alcoholism | 11.1% | 5% | **2.4 (1.6, 3.6)** | 3.1% | 5.4% | 0.6 (0.1, 2.3) | 4.8% | 5.4% | 0.9 (0.4, 1.9) |

\* Analysis done using CHI square and simple logistic regression. Data expressed as % unless otherwise specified

\*\*Not employed included students, house wife, inmates, and retirees

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| Table S2: Demographic features and clinical presentation of 4,215 TB patients in the validation data set by adverse outcomes and drug resistance status in Tamaulipas Mexico 2006- 2013 \* | | | | | | | | | |
|  | Death | | | Treatment failure | | | Drug Resistance | | |
| Characteristics | Yes (n=260) | No | OR (95%CI) | Yes (n= 93) | No | OR (95%CI) | Yes (n=259) | No | OR (95%CI) |
| Age (mean, ± SD) | 50.2 (18.9) | 42.3 (16.2) | **1.02 (1.01, 1.03)** | 43.3 (14.9) | 43.1 (16.5) | 1.0 (0.9, 1.01) | 41.8 (15.8) | 43.1 (16.5) | 0.9 (0.9, 1.0) |
| Gender |  |  |  |  |  |  |  |  |  |
| Female | 30.8% | 35.5% | 1 | 23.7% | 35.5% | 1 | 32.5% | 35.3% | 1 |
| Male | 69.2% | 64.5% | 1.2 (0.9, 1.6) | 76.3% | 64.5% | **1.8 (1.1, 2.9)** | 67.5% | 64.7% | 1.1 (0.8, 1.7) |
| Education |  |  |  |  |  |  |  |  |  |
| Higher than primary school | 27.2% | 43.1% | 1 | 34.4% | 42.3% | 1 | 45.9% | 42% | 1 |
| No or primary school | 72.8% | 56.9% | **2.0 (1.5, 2.7)** | 65.6% | 57.7% | 1.4 (0.9, 2.2) | 54.1% | 58% | 0.9 (0.7, 1.3) |
| Employment Status |  |  |  |  |  |  |  |  |  |
| Employed | 29.8% | 43.5% | 1 | 37.1% | 42.8% | 1 | 43.6% | 42.7% | 1 |
| Not employed\*\* | 44.7% | 42% | **1.6 (1.1, 2.2)** | 35.7% | 42.3% | 0.9 (0.6, 1.7) | 39.4% | 14.3% | 0.9 (0.6, 1.4) |
| Unemployed | 25.5% | 14.5% | **2.6 (1.7, 3.9)** | 27.1% | 14.8% | **2.1 (1.1, 3.8)** | 17% | 15.1% | 1.1 (0.6, 1.9) |
| BCG Vaccine (yes) | 61.7% | 77.4% | **0.5 (0.4, 0.6)** | 77.8% | 76.5% | 1.1 (0.6, 1.8) | 82.7% | 76.3% | 1.5 (0.9, 2.4) |
| Location of disease |  |  |  |  |  |  |  |  |  |
| Extra-pulmonary | 15% | 7.9% | 1 | 0% | 8.5% | N/A | 0.9% | 8.5% | 1 |
| Pulmonary | 85% | 92.1% | **0.5 (0.3, 0.7)** | 100% | 91.5% | N/A | 99.1% | 91.5% | **10.5 (1.5, 75.7)** |
| MDR (yes) | 0% | 0.5% | N/A | 14% | 0.2% | **95.5 (37, 245)** | N/A | N/A | N/A |
| Positive initial AFB smear | 77.5% | 84.7% | **0.6 (0.4, 0.9)** | 94.6% | 84% | **3.3 (1.3, 8.3)** | 95.4% | 83.9% | **4.0 (1.6, 9.9)** |
| Number of bacilli in initial AFB smear |  |  |  |  |  |  |  |  |  |
| Negative | 22.6% | 15.4% | 1 | 5.4% | 16.1% | 1 | 4.6% | 16.1% | 1 |
| Rare bacilli (+1) | 28.1% | 37.6% | **0.5 (0.3, 0.8)** | 33.3% | 37.1% | **2.7 (1.0, 6.9)** | 31.8% | 37.2% | **3.0 (1.2, 7.8)** |
| Few to moderate (> +2) | 49.3% | 47% | 0.7 (0.5, 1.0) | 61.3% | 46.8% | **3.9 (1.6, 9.8)** | 63.6% | 46.7% | **4.8 (1.9, 12)** |
| Comorbidities |  |  |  |  |  |  |  |  |  |
| Diabetes | 16.5% | 25.7% | **0.6 (0.4, 0.8)** | 30.1% | 25% | 1.3 (0.8, 2.0) | 34.2% | 24.9% | **1.6 (1.1, 2.3)** |
| HIV | 18.9% | 4.3% | **5.2 (3.7, 7.3)** | 3.2% | 5.2% | 0.6 (0.2, 1.9) | 3.5% | 5.2% | 0.7 (0.2, 1.8) |
| Malnutrition | 14.2% | 7% | **2.2 (1.5, 3.2)** | 9.7% | 7.4% | 1.3 (0.7, 2.7) | 3.5% | 7.5% | 0.4 (0.2, 1.2) |
| Alcoholism | 8.9% | 5.7% | **1.6 (1.0, 2.5)** | 8.6% | 5.8% | 1.5 (0.7, 3.2) | 3.5% | 6% | 0.6 (0.2, 1.6) |

\*Analysis done using CHI square and simple logistic regression. Data expressed as % unless otherwise specified

\*\*Not employed included students, house wife, inmates, and retirees

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| Table s3: Summary of models and estimated proportion of TB patients that would benefit from enhanced monitoring in order to prevent adverse treatment outcomes in Tamaulipas | | | | | | |
| Adverse outcome | | **c-statistic** | **Optimal modified risk score cut-off** | **Sensitivity** | **Specificity** | **% of all TB patients ≥ cut-off** |
| Treatment failure | | 0.74 | 15 | 52% | 66% | 34.4% |
| Drug resistance | | 0.61 | 9 | 33% | 74% | 58.4% |
| Death | | 0.77 | 5 | 60% | 71% | 47.6% |
| \* Cut-offs, sensitivity and specificity based on Liu method (Table 3) | | | | | |  |
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| Table s4: Summary of models and estimated proportion of TB patients that would benefit from enhanced monitoring in order to prevent adverse treatment outcomes in Tamaulipas, Mexico | | | | | |
| Adverse outcome | **Risk score cut-offs** | | **Observed proportion of adverse outcome in validation data set** | **% of all TB patients with constructed score w/thin this cut-off** | |
| Treatment failure | 0-23 | | 5% | 99.5% | |
|  | 40-50 | | 58% | 0.2% | |
|  | > 50 | | 78% | 0.3% | |
| Drug resistance | < 8 | | 0% | 1.1% | |
|  | 8 | | 2.2% | 22.5% | |
|  | 9 | | 3.4% | 50.4% | |
|  | 10 | | 4.2% | 25.9% | |
| Death | 0-4 | | 3.5% | 52.4% | |
|  | 5-9 | | 8% | 44.7% | |
|  | 10-12 | | 14.5% | 2.6% | |
|  | 13-16 | | 31% | 0.3% | |

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| Table S5: Characteristics of TB patients with positive adverse outcomes by score cutoff point in Tamaulipas Mexico 2006- 2013\* | | | | | | | | | |
| Characteristics | Death risk score | | | Treatment failure risk score | | | Drug resistance risk score | | |
|  | < 5 (n=121) | ≥ 5 (n=400) | OR (95%CI) | < 15 (n= 51) | ≥ 15 (n= 92) | OR (95%CI) | < 9 (n=32) | ≥ 9 (n=204) | OR (95%CI) |
| Age (mean, ± SD) | 36.6 (11.9) | 54.8 (18.2) | **1.1 (1.0, 1.1)** | 41.8 (13.5) | 48.4 (16.1) | 1.03 (1.0, 1.05) | 53.3 (9.4) | 39.7 (15.6) | **0.9 (0.92, 0.97)** |
| Gender |  |  |  |  |  |  |  |  |  |
| Female | 50.4% | 18.3% | 1 | 19.6% | 29.3% | 1 | 37.5% | 29.9% | 1 |
| Male | 49.6% | 81.8% | **4.6 (2.9, 7.1)** | 80.4% | 70.6% | 0.6 (0.3, 1.3) | 62.5% | 70.1% | 1.4 (0.6, 3.0) |
| Education |  |  |  |  |  |  |  |  |  |
| No or primary school | 55.4% | 73.4% | **2.2 (1.4, 3.4)** | 54.9% | 77.2% | **2.8 (1.3, 5.8)** | 56.2% | 55.6% | 0.9 (0.5, 2.1) |
| Higher than primary school | 44.6% | 26.6% | 1 | 45.1% | 22.8% | 1 | 43.8% | 44.4% | 1 |
| Employment Status |  |  |  |  |  |  |  |  |  |
| Employed | 32.9% | 38.4% | 1 | 53.8% | 36.5% | 1 | 53.3% | 42.2% | 1 |
| Not employed\*\* | 52.3% | 35.9% | 0.6 (0.3, 1.0) | 30.8% | 40.5% | 1.9 (0.8, 4.9) | 43.3% | 40.0% | 1.1 (0.5, 2.4) |
| Unemployed | 14.8% | 25.7% | 1.5 (0.7, 3.1) | 15.4% | 23.0% | 2.2 (0.7, 6.6) | 3.3% | 20.8% | **7.9 (1.0, 61.9)** |
| BCG Vaccine (yes) | 69.2% | 62.5% | 0.7 (0.5, 1.2) | 81.3% | 81.0% | 0.9 (0.4, 2.5) | 89.7% | 81.3% | 0.5 (0.1, 1.7) |
| Location of disease |  |  |  |  |  |  |  |  |  |
| Extra-pulmonary | 21.5% | 12.7% | 1 | 0 | 0 | N/A | 0.0% | 0.0% | N/A |
| Pulmonary | 78.5% | 87.3% | **1.9 (1.1, 3.2)** | 100% | 100% | N/A | 100.0% | 100.0% | N/A |
| MDR (yes) | 0.0% | 1.3% | N/A | 0.0% | 30.4% | N/A | N/A | N/A | N/A |
| Positive initial AFB smear | 75.3% | 78.5% | 1.2 (0.7, 2.1) | 100% | 100% | N/A | 100.0% | 100.0% | N/A |
| Comorbidities |  |  |  |  |  |  |  |  |  |
| Diabetes | 17.4% | 16.7% | 0.9 (0.6, 1.6) | 29.4% | 31.5% | 1.1 (0.5, 2.3) | 59.4% | 28.9% | **0.3 (0.1, 0.6)** |
| HIV | 0.0% | 24.8% | N/A | 3.9% | 3.3% | 0.8 (0.1, 5.1) | 3.1% | 3.9% | 1.3 (0.2, 10.5) |
| Malnutrition | 2.5% | 21.7% | **10.9 (3.4, 35.2)** | 11.8% | 8.7% | 0.7 (0.2, 2.2) | 0.0% | 6.9% | N/A |
| Alcoholism | 0.8% | 12.7% | **17.5 (2.4, 128.3)** | 9.8% | 5.4% | 0.5 (0.1, 1.9) | 3.1% | 3.9% | 1.3 (0.2, 10.5) |

\*Data expressed as % unless otherwise specified

\*\*Not employed included students, house wife, inmates, and retirees